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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/693,120
Filing Date: October 20, 2000
Appellant(s): LEE ET AL.

Paul Clark
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 18, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

Examiner also adds that US Serial No. 09/692,664 is a related case that is on appeal.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that all claims do stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,782,971	Constantz et al	7-1998
5,085,861	Gerhart et al	2-1992

.Yamamura et al, "Antitumor Effects and Distribution of Adriamycin Incorporated into Hydroxyapatite Implants in a Cancer Rat Model Bearing Swarm Rat Chondrosarcoma."JPN. 65, (1994) pages 289-291.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamura et al (JPN. J. Pharamcol 65, 289-291 (1994), IDS filed on 12/6/2002) In view of Gerhart et al US Patent 5,085,861 and Constantz et al US Patent 5,782,971.

The instant claims are directed to paste compositions comprising calcium phosphate and an anticancer and kits thereof containing a second adjuvant and means to deliver the composition.

Yamamura discloses methods of implanting injectable doxorubicin loaded hydroxyapatite beads for treating tumor (abstract, entire page 289-291). The Ca/P raion of Yamamura's composition is 1.68. Yamamura does not specifically teach a paste formulation.

Gerhard disclose calcium phosphate containing compositions comprising biocompatible calcium phosphate ceramics that can be in the form of an injectable or moldable paste and will solidify within 10 minutes after administration. (see abstract; col 7, lines 30-46, 60-67; col 8, lines 1-20; examples 2-3). The particle size of Gerhard's compositions falls within the instantly claimed nanocrystalline (see col 7, lines 15-25). Gerhard's compositions contain active agents that are readily used in treatment of cancers such as bone tumor (col 13, lines 45-67). Gerhard finally discloses kits for

preparing his composition for ease of use in a clinical or surgical setting (col 7, lines 42-49).

Constantz et al teach amorphous calcium phosphate containing compositions that are used as suitable drug delivery vehicles (col 2, lines 60-67; col 6, lines 61-63). Constantz specifically teaches paste formulations of calcium phosphate that are capable of hardening after administration at the site of interest (col 6, lines 40-64). Constantz's composition comprise about 15 wt% of the dry ingredient (solid component) having particle sizes of about 0.5- 500 microns (col 5 lines 1-3; and lines 14-25). Constantz further indicates that one of ordinary skill in the art would be able to modify the viscosity of his composition by varying the percentages of solids in his composition, thus allowing for ease of administration (col 6, lines 32-39). Constantz suggests the use of an additional calcium phosphate and also states that the calcium to phosphate ratio of such compositions should be about 1.6 to about 1.8 (see col 3, lines 5-20; col 5, lines 1-10, claims 1-5). Constantz finally suggests preparing kits to ease access and preparation (see col 7, lines 1-10). Constantz lacks the specific teaching of an anticancer agent in combination with the calcium phosphate vehicle.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of invention to modify physical characteristics of Yammmura's composition into an injectable paste, as suggested by Gerhard and Constantz, and formulate a hardenable calcium phosphate formulation that is easily administered to a site of interest such as a tumor, because the ordinary artisan would have had a reasonable expectation of success in achieving the same results. Finally, the ordinary artisan would have had a

reasonable expectation of success in preparing a ready to use kit for easing the access and use of such compositions at a clinical setting.

Claims 22-44 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-44 of copending Application No. 09/692,664 for the reasons of record.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both claimed inventions are directed towards compositions comprising calcium phosphate and an anticancer agent. The only difference between the two applications is that the instant claims use nanocrystalline or poorly crystalline calcium phosphate. Nevertheless, it would have been obvious to one of ordinary skill in the art at the time of invention to practice the instant invention using any species of calcium phosphate including the instant nanocrystalline or poorly crystalline calcium phosphate, because the ordinary artisan would expect the same clinical outcome.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

(11) Response to Argument

Appellant's arguments have been fully considered but they are not persuasive, because Appellant has not met their burden of proof required to overcome the rejections of record. Appellant's arguments lacks scientific and legal support. Accordingly, the rejections of record should be maintained.

Appellant's arguments merely amounts to attacks against the references individually. However, it is well settled that one cannot show nonobviousness by

attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the instant case, all elements of claimed inventions are described by the cited prior art. The cited references also set forth that the state of art provides ample expectation of success to prepare a paste like formulation containing an anticancer agent, because such a type of carrier is readily used for delivery of various drugs as described by Gerhart and Constantz. Further, Appellant has not shown any unexpected results or benefits when a past-like formulation is used as the carrier system for an anticancer agent. Thus, Appellants have not met their burden of proof of showing the nonobviousness of the instant claims over the cited references.

Appellant argues that the combined references fail to teach or suggest compositions containing a calcium phosphate paste in combination with an anticancer agent. (see Brief at page 9). In response Examiner states that Appellant's position that the combined teachings does not meet the limitations of the instant claims, is not correct. Both the primary and secondary references provide for such teachings and their combined teachings meet all the limitations of the instant claims.

As the initial matter, the primary reference, Yamamura teaches the use of a typical anticancer agent, doxorubicin, which is within the scope of the instant claims. Yamamura teaches the combination of doxorubicin with an injectable hydroxyapatite (calcium phosphate) bead carrier system. (see abstract). The secondary references, Gerhart and Constantz, teach various forms of calcium phosphate carrier systems

including the paste formulations. Therefore, their combined teachings meet all elements of the instant claims.

Second, Applicant's arguments that none of the cited references *per se* teaches an anticancer agent in a calcium phosphate delivery system is not correct, because aside from the use of doxorubicin drug by the primary reference, the secondary references teach a combination of calcium phosphate paste with an agent which falls within the scope of the instantly claimed "anticancer agents."

To establish the scope of the term "anticancer agent," Examiner states that throughout the prosecution, such term is given its broadest reasonable interpretation. Accordingly, Examiner takes the position that the instant limitation "anticancer agents" encompass all medications that may be used during the course of treating a tumor or a cancer, because the definitions of such term in the specification is not exclusive of antibiotics.

To ascertain the scope of the term "anti-cancer agent" Examiner has considered this limitation in view of the Specification. The Specification describes the scope of the term "anticancer agents" at page 14, lines 8-20. Accordingly, "[S]uitable anticancer agents may be one or more of known chemotherapy drugs such as methotrexate, cis-platin, prednisone, doxorubicin... etc." Certainly the only utility of such recited agents are not for treating cancer. For example, prednisone is also a known anti-inflammatory agent. Methotrexate or Cisplatin is readily used for treating rheumatoid arthritis. Doxorubicin is a well-known anthracycline antibiotic. Thus, the term "known

chemotherapy drugs" is inclusive of many agents that have utilities other than merely for cancer treatment, including antibiotics.

Further, "chemotherapy" is viewed by the Examiner to mean; treating a disease with chemical agents. Thus, contrary to Appellant's position the term anticancer agent is not viewed to *per se* exclude antibiotics, because the language of "known chemotherapy drugs" or "anticancer agents" as interpreted in view of the specification and the general knowledge in the art, does not *per se* exclude antibiotics.

Further, to overcome a rejection of record, Appellant has previously argued on the record that "All that is required to practice the claimed invention is the ability to mix the two components [the calcium phosphate and anticancer agent] together. The claim does not require that the composition actually treats the tumor." (see Appellant's submission filed on March 5, 2003 at page 6, lines 1-10). Therefore, the point of novelty is viewed as to whether doxorubicin of Yamamura may be used in combination with a calcium phosphate paste of the secondary references.

In the absence of a clear indication in the Specification as to what is encompassed by the term "anticancer agents," and Appellant's assertion that the instantly claimed composition does not require the actual treatment of a tumor; Examiner has viewed the scope of such term to include any medication that can be used during a treatment course of a tumor or a cancer. Such medication can include antibiotics or any other medication reasonably used in the art for such purpose. Thus, Appellant's position that none of the cited references teaches an anticancer agent, is not correct.

In addition, the rejection at issue relies on the teachings of Yamamura as a primary reference. Yamamura uses a typical anticancer agent such as doxorubicin in treating a cancer rat model bearing rat chondrosarcoma which is a tumor derived from cartilage. (see abstract, 2nd col at page 436). Yamamura goes on to conclude that implantation of doxorubicin may be useful in delivering drugs in the site of a bony defect after surgical removal of a bone tumor. (see the last two lines of the abstract, and the last two lines of the article at page 438). Doxorubicin is itself an anthracycline antibiotic. (see for example page 437, 3rd paragraph of Yamamura, which substantiates what is already known in the art about Doxorubicin being an antibiotic anticancer agent).

The secondary references teach calcium phosphate formulations in paste form for injection. As explicitly indicated in page 4, line7 of the Office Action filed on August 7, 2002, Gerhart suggests the use of a moldable paste containing calcium phosphate in treatment of bone tumors to avoid complications associated with such treatments (see col 13, lines 45-67).

Constantz also teach various forms of calcium phosphate carrier system in paste type formulations. Constantz, for example, indicates that one of ordinary skill in the art would be able to modify the viscosity of his composition by varying the percentages of solids in his composition, thus allowing for ease of administration (col 6, lines 32-39). Therefore, the use of an antibiotic anticancer agent of Yamamura, in place of the antibiotics of Gerhart and Constantz; or the use of the injectable calcium phosphate paste carrier systems of Gerhart and Constantz in place of the injectable bead carrier system of Yamamura would have been suggested by the cited references.

Appellant argues that interpretation of Examiner about the use of Gerhart's composition is incorrect, because Gerhart teaches bone cement containing antibiotic and not any agent that would be used to treat the tumor itself (see Brief at page 10, 1st para.).

In response, Examiner states that such line of arguments are not commensurate with the scope of the claims, because as argued above, the term "anticancer agents" used instantly does not exclude medications that can be used during the course of treatment of a tumor. As suggested in Gerhart, the course of treatment of a bone tumor includes administration of antibiotics including avoidance of future complications. (see col 13, lines 45-67). Yamamura teaches doxorubicin as such agent. Thus, there is ample suggestion in the art to treat any useful agent that can be used for treatment of bone tumor. Therefore, using doxorubicin, for example, in the paste formulation as described Gerhart and Constantz would have been obvious.

Appellant also argues that Constantz provide no motivation to combine their teachings with Yamamura. (see Brief at page 10, last two paras.).

In response, examiner states that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Aside from the fact that Gerhart explicitly suggest the use of hydroxyapatite paste formulation in treatments of bone tumor, Examiner adds that the teachings, suggestions or motivation to modify Yamamura's formulation can also be inferred from the knowledge generally available to one of ordinary skill in the art supplied by Gerhart and Constantz. Gerhart and Constantz clearly set forth the state of art in preparing paste carrier systems of hyrdoxyapatite formulations for delivering a drug to a site of interest.

Constantz clearly indicates that one of ordinary skill in the art would be able to modify the viscosity of his composition by varying the percentages of solids in his composition, thus allowing for ease of administration (col 6, lines 32-39). Additionally, the general state of art merely relies on mixing a carrier system and an active drug. Examiner views such general knowledge not to be complex and well within the purview of an ordinary skill in the art. Accordingly, the teachings, suggestions and motivation to do the modification is described in the knowledge generally available to one of ordinary skill in the art of pharmaceutical formulations and drug delivery systems.

Further, Examiner points out that obviousness does not require absolute predictability of success. For obviousness under §103, all that is required is a reasonable expectation of success. *In re Longi*, 759 F.2d 887, 897, 225 USPQ 645, 651-52 (Fed. Cir. 1985); *In re Clinton*, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976). There is always at least a possibility of unexpected results that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious. *In re Merck & Co .*, 800 F.2d at 1098, 231 USPQ at 380; *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co .*, 730 F.2d

1452, 1461, 221 USPQ 481, 488 (Fed.Cir. 1984). Here, Appellant simply has failed to meet the burden of proving nonobviousness.

Again, Examiner views the nature of the art of mixing a pharmaceutical agent such as doxorubicin in a paste like formulation not to be complex. Further, both doxorubicin formulation of Yamamura and the paste formulations of Gerhart, Constantz and Poser are used for their own intended purpose. Thus, Examiner has met his burden of showing at least a predictability of success when doxorubicin is mixed with a hydroxyapatite paste formulation in the manner described by Gerhart and Constantz. Appellant has not produced any unexpected results to show why such expectation would have been unexpected in the art. Therefore, Appellant has not met his burden of proving nonobviousness.

Appellant also argues that none of the cited references, either explicitly or implicitly teaches or suggests that an anticancer agent could be used in place of the antibiotic/antimicrobial agent. (see page 12, 1st para.).

Such line of arguments is scientifically and legally flawed on its face, because Doxorubicin is itself an anthracycline antibiotic that is used as an anticancer agent. (see Yammamura at page 437, 3rd para.). Thus, substituting the drug of Gerhart and Constantz with the doxorubicin of Yamamura would have been at least implicitly described in the art.

Appellant alleges that the examiner's conclusion of obviousness is based upon improper hindsight reasoning. (see Brief at pages 12-13).

In response Examiner states that it is well established that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In the instant case, the teachings that are relied upon in the rejection of record account for the knowledge within the level of ordinary skill in the art at the time of the claimed invention. Examiner also provided support as to the motivation and the expectation of success when combining the teachings of the cited references to produce at least the same results as the Yamamura's formulations. The teachings of the cited references either published or was filed or published prior to the effective filing date of the instant application. Thus, the knowledge relied therein was well available to one ordinary skill at the time of the claimed invention and the person of ordinary skill in the art had reasonable expectation of success in creating a doxorubicin formulation comprising doxorubicin and a hydroxyapatite in a paste formulation. Accordingly, the rejection is not based on improper hindsight, rather *prima facia* obviousness.

Appellant also has argued that claims 42-44 are not obvious for the reasons set forth in pages 14-15 of the Brief. Since Appellant acquiesces that claims stand or fall together at page 5 of the Brief, patentability of all the pending claims are assessed based on claim 22. Accordingly, Examiner relies on all the arguments that are presented above to rebut Appellant's position on claims 42-44.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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ss
September 29, 2004

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